Research Article

Right Ventricular Reverse Remodeling after Catheter-Directed Thrombolysis for Sub-massive Acute Pulmonary Embolism: A Prospective Single Arm Single Center Trial

Abdelmaksoud A. Elganady*, Abeer M. Shawky* and Ahmed Dawood**
* Department Cardiology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
** Department Cardiology department, National Heart Institute, Cairo, Egypt

Abstract
Background: Pulmonary embolism (PE) represents a major threat for the life and well-being of a large number of patients worldwide. Once a diagnosis of PE is made, patients should receive appropriate treatment without delay. Massive PE is treated with thrombolytic therapy and low risk PE is treated with anticoagulation. In patients with acute sub-massive pulmonary embolism, although systemic thrombolysis improves right ventricular (RV) dilatation but it is associated with major bleeding, and is withheld in many patients at risk. This single arm single center study investigated whether catheter-directed thrombolysis (CDT) improve right ventricular dilatation, function and pulmonary artery pressure (reverse right ventricular remodeling) without increase in major bleeding. **Methods and Results:** Twenty five patients with acute sub-massive PE and mean age of 55±04 years were included in this study. Sixty % of the study subjects were male. Eligible patients had right ventricular dysfunction on echocardiography and elevated ProBNP as well as myocardial injury as detected by cardiac biomarkers (positive test for cardiac troponin T). The CDT regimen of 1 mg per lung per hour recombinant tissue plasminogen activator (rapt) over 12 hours (24 mg rtPA for bilateral PE and 12 mg for unilateral PE) via the ultrasound assisted infusion catheter (EKOS) or Pigtail catheter (n=7; EKOS infusion catheter and n=18; Pigtail catheter). Primary outcomes were change in right ventricular end diastolic diameter (RVEDD), right ventricular end-diastolic dimeter/left ventricular end-diastolic dimeter ratio (RVEDD/LVEDD ratio), right ventricular systolic function (RV-TAPSE and TASV) and the systolic pulmonary artery pressure (sPAP) from baseline to 48 hours after CDT. Safety outcomes included all-cause mortality and the treatment-associated morbidity (i.e. major and minor bleeding). Outcomes was reported at time points of 48 hours and 90 days after treatment. The average echocardiographic RVEDD were reduced from 4.8 cm to 4 cm which is statistically significant (P < 0.05), RVEDD/LVEDD ratio decreased from 1.1 (range from 0.9 to 1.6) at baseline to 0.9 (range from 0.8 to 1.2) at 48 hours (P < 0.001), the RV-TAPSE was 1.3 cm and increased to 1.8 cm 48 hours after CDT (P value < 0.05) and the RV-TASV was 7.9 cm/s and increased to 10.5 cm/s 48 hours after CDT (P value < 0.001), and sPAP reduced from 50.22 mmHg (Range from 26 to 100 mmHg) before treatment to 33.3 mmHg (Range from 20 to 93 mmHg) (P value < 0.05) 48 hours after treatment. Within 90 days after CDT, only 3 minor bleeding episodes but no hemodynamic decompensation, recurrent venous thromboembolism, major bleeding complications or death. **Conclusion:** CDT improves (reverses) right ventricular remodeling in patients with acute sub-massive PE effectively and safely. Future studies will further define the role of CDT in comparison to other revascularization strategies in the management of PE patients at increased risk.
Keywords: Pulmonary embolism (PE), thrombolytic therapy, catheter-directed thrombolysis (CDT)

Introduction
Acute pulmonary embolism (PE) represents a major threat for the life and well-being of a large number of patients worldwide.[1]

Once a diagnosis of PE is made, patients should receive appropriate treatment without delay. This can be achieved by risk

stratification and an associated escalation of the degree of aggressiveness of treatment.[2]

The American Heart Association (AHA) classifies pulmonary embolism into low-risk "non-massive", intermediate-risk "sub-massive" and high-risk "massive" categories.[3] **Massive (high-risk)** PE is defined as acute PE with persistent systemic arterial hypotension (systolic blood pressure < 90 mmHg) for > 15 minutes or the requirement of inotropic support to maintain SBP >90 mm Hg. Other high-risk markers of massive PE include pulseless, or profound bradycardia with symptoms of cardiogenic shock, or the need for cardiopulmonary resuscitation; the in-hospital mortality rate may exceed 50%.[4] **Sub-massive (intermediate-risk)** PE is defined as acute PE occurring in normo-tensive patients (systolic blood pressure ≥ 90 mmHg) with evidence of right ventricular (RV) dysfunction by echocardiography or computed tomography (CT) scan with elevated proBNP and evidence of myocardial injury by elevated cardiac biomarkers (troponin I or T); the in-hospital mortality ranges between 6% and 8%.[5] Right ventricular dysfunction is further defined as RV systolic dysfunction on echocardiography, RV dilation (right ventricle diameter divided by left ventricle diameter > 0.9 in the 4-chamber view by echocardiogram or CT), elevated brain natriuretic peptide (BNP) > 90 pg/mL and electrocardiogram (ECG) changes. Other markers of sub-massive PE include tachycardia, tachypnea, and hypoxia, which may be less specific and thus less helpful in management selection. Special attention should be given to patients who had syncope, which may represent transient hemodynamic instability and the potential for higher risk. Finally, l**ow-risk (non-massive PE)** is defined as patients with hemodynamically stable acute PE and have neither right ventricular dysfunction nor elevated cardiac biomarkers; these patients usually have excellent short-term prognosis once therapeutic levels of anticoagulation are established.[6] The European Society of Cardiology (ESC) guidelines recommend further risk stratification of the interme-diate-risk group into intermediate-low and intermediate-high–risk subgroups, with the latter defined by the presence of evidence of RV dysfunction and markers of myocardial injury.[7]

Despite a high case fatality rate, most patients with massive and sub-massive PE continue to be treated conservatively with anticoagulation alone. Conventional anti-coagulant treatment for acute pulmonary embolism effectively prevents thrombus extension and recurrence, but does not dissolve the clot. On the other hand, full-dose systemic thrombolytic therapy was shown to prevent potentially life-threatening haemodynamic decompensation or collapse in these patients, but this benefit was counterbalanced by a high risk of hemorrhagic stroke or major non-intrac-ranial bleeding.[8] Accordingly, systemic thrombolysis is not routinely recommended as primary treatment for those patients, but should be considered if clinical signs of hemodynamic decompensation appear.

Surgical pulmonary embolectomy or percu-taneous catheter-directed thrombolysis (CDT) may be considered as alternative, for patients with sub-massive PE, in whom haemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high **"rescue procedures"**.[9] CDT is an increasingly used treatment option, based largely on the assumptions that it is more efficacious than anticoagulation alone and safer than systemic thrombolysis.[10] It is a treatment modality that actively removes the obstructing thrombi from the main or lower lobe pulmonary arteries to achieve rapid reperfusion of the pulmonary arteries, to facilitate right ventricular recovery, and to improve symptoms and survival.
Therefore, this catheter-directed interve-ntion results in hemodynamic improvement with restoration of RV hypokinesis, normalization of RV size and reduction of abnormally high pulmonary arterial pressures. Intrapulmonary administration of thrombolytic agents may potentially promote intravascular fibrinolysis elsew-here in the pelvis or lower extremity, thereby, reducing the likelihood of recurrent venous thromboembolism.
Another therapeutic advantage of this intervention includes potential reduction of

Right Ventricular Reverse Remodeling after Catheter-Directed Thrombolysis for Sub-massive Acute Pulmonary

chronic elevations of pulmonary vascular resistance by improving pulmonary capillary blood flow, which might theoretically lower the incidence of long-term pulmonary hypertension.[11]

Aim of the Work
This single arm single center prospective trial investigated whether catheter-directed thrombolysis (CDT) can reverse right ventricular remodeling by improving right ventricular dilatation, function and pulmonary artery pressure without increase in morbidity and mortality in patients with sub-massive pulmonary embolism (PE).

Methods
Patients and Study Design:
From November 2015 to January 2018; 25 patients from Dr Erfan and Bagedo general hospital in Jeddah were included in a prospective single arm single center for CDT for acute sub-massive PE. The CDT regimen of 1mg per lung per hour recombinant tissue plasminogen activator (rtPA) over 12hours (24 mg rtPA for bilateral PE and 12mg for unilateral PE) via the ultrasound assisted catheter (EKOS) infusion catheter or Pigtail catheter (n=7; EKOS infusion catheter and n=18; Pigtail catheter). Clinical data including symptoms, vital signs, comorbidities, risk factors for venous thromboembolism and common laboratory values were recorded. All patients provided written informed consent before enrollment.

Inclusion criteria:
Patients were eligible for CDT if they had acute sub-massive PE and evidence of embolus located in at least one main or lower lobe pulmonary artery as assessed by contrast-enhanced chest computed tomography (CT) or conventional pulmonary angiograph. Patients with elevated proBNP and evidence of right ventricular (RV) dysfunction by echocardiographic apical 4-chamber view; including increase RVEDD, increase RVEDD/RVEDD ratio more than or equal 0.9. Patients with evidence of myocardial injury as detected by elevated cardiac biomarkers (troponin T).[2,4]

Exclusion criteria:
Index PE symptom duration >14 days; insufficient echocardiographic image quality in the apical 4-chamber view that prohibited the measurement of the RV/LV ratio; known significant bleeding risk; active bleeding; known coagulation disorder; platelet count <100 000/mm3; previous use of vitamin K antagonists with international normalized ratio >2.5 on admission; history of any intracranial or intraspinal surgery or trauma or bleeding; intracranial neoplasm, arteriovenous malformation, or aneurysm; gastrointestinal bleeding <3 months; internal eye surgery or hemorrhagic retinopathy <3 months; or major surgery.

Study outcomes:
Primary outcomes in the present study were improvement in right ventricular end diastolic diameter (RVEDD), right ventricular end-diastolic dimeter/left ventricular end-diastolic diameter (RVEDD/LVEDD) ratio, right ventricular systolic function (TAPSE and TAVS) and systolic pulmonary artery pressure (sPAP) from baseline to 48 hours after treatment. Safety outcomes included all-cause mortality and the treatment-associated morbidity (i.e. major and minor bleeding). Outcomes was reported at time points of 48 hours and 90 days after treatment. Major hemorrhage was defined as overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to the bleed); or bleeding requiring surgical intervention for control or bleeding requiring vasoactive drugs or bleeding causing intracranial hemorrhage.

Imaging Assessment of Severity of PE: Echocardiography:
Transthoracic echocardiography was performed at baseline and after the completion of CDT at 48 h. Recorded echocardiographic loops were analysed by an experienced non invasive cardiologist for signs of right ventricular dysfunction.[12] Right and left ventricular end diastolic dimensions were obtained from the end-diastolic apical four-chamber image by measuring the ventricular endocardial borders at the sub-annular plane located 1cm above the

annular plan and perpendicular to the inter-ventricular septal axis.[4] The difference in RV/LV ratio from baseline to 48 hours was the primary end point, particular attention was paid to obtain at least 3 adequate cine loops from the apical 4-chamber view for the measurement of RV/LV ratio. A RV/LV ratio $\geq$ 0.9 was an inclusion criterion. In addition, from the apical 4-chamber views, right ventricular systolic function (RV-TAPSE and TASV) and the systolic pulmonary artery pressure (sPAP) from baseline to 48 hours after CDT were obtained.

Contrast-Enhanced Chest CT:
All computed tomographic pulmonary angiography (CTPA) scans were performed using a Siemens Somatom AST and Toshiba Aquillion One. The acquisition was performed from the diaphragm to lung apices in supine position, during a single breath-hold or shallow breathing, depen-ding on the patient's level of dyspnea. The baseline chest CT scans confirmed the presence of PE in all enrolled patients.

Procedure of Standard catheter-directed thrombolysis (CDT):
The insertion of the catheter system was performed at the cardiac catheterization laboratory with continuous hemodynamic and electrocardiographic monitoring. Venous access was obtained at the common femoral vein with the use of one or two 6F introducer sheath for patients who were scheduled for unilateral or bilateral CDT. Unilateral or Bilateral multipurpose catheter placement was performed in case of embolus located in both main and proximal lower lobe pulmonary arteries. Contrast injection into the main PA or selectively into each PA was performed to identify the location of the thrombi; these were typically in the main and/or lower main PA branch. If the location of the thrombi was not clear by manual injection, or the anatomy had not been previously established by CT, and if the pulmonary pressure was not severely elevated, a power injection was necessary (e.g., at 15 to 20 m/s for a total of 30 ml selectively in each main PA, with a 15 to 20 left anterior oblique projection for the left PA and 0 to

20 right anterior oblique projection for right PA). The amount of iodine contrast agent was kept as low as possible and depended mainly on the hemodynamic status and the size of the selected vessel. Nonselective angiography with large (>30 mL) amounts of contrast agent via power injector was avoided due to the risk of worsening right ventricular failure. To minimize the risk of pulmonary artery perforation, the main and lower lobe pulmonary arteries was considered for treatment, and segmental branches with a diameter of <6 mm was not approached. [13]

An exchange soft-j-tipped long wire was placed in the lower PA branch, and the diagnostic catheter was exchanged for an infusion catheter, which had a treatment zone of 6, 12,18,24,30,40 and 5o cm through which t-PA was infused into the clot. A second infusion catheter was placed in the contralateral PA through a second venous sheath, if needed, using the same technique. Unilateral or Bilateral EKOS Catheter was advanced inside each infusion catheters. rtPA slowly infused through the catheter simultaneously with emission of ultrasonic wave from EKOS catheter, which is left in place for the duration of the treatment. Systemic arterial oxygen satu-ration was recorded through transcutaneous oxygen saturation measurement. A 6 F pig tail catheter used if EKOS catheter was not available for local delivery of rtPA without ultrasonic source. A continuous infusion of rTPA at 1 mg per lung per hour and of saline coolant at 35 mL/h per catheter was initiated. After catheter placement, patients were transferred to the intensive care unit for continuous monitoring for the remaining 12 hours. The maximum suggested rtPA dose was 24 mg. During infusion of rt-PA, intravenous unfractionated heparin or low molecular weight heparin was continuously administered simultaneously with rtPA infusion. Thereafter, the infusion catheter was removed with or without fluoroscopic guidance in the intensive care unit. Follow-up systemic arterial oxygen saturation was obtained. Finally, after completion of rtPA and discontinuation of heparin or low molecular weight heparin, the introducer sheath was removed, and the puncture site

manually compressed until local haemostasis was achieved.

Statistical Analysis

Data were entered in Microsoft Excel and then converted to an SPSS version for statistical analysis. Data are presented as maximum/minimum and average with means ± standard deviations as median values with ranges or absolute numbers and percentages for continuous and categorical variables, respectively. *P*-values for differences between before and after CDT were calculated from unpaired *t*-tests.

Results

This study is a prospective single arm single center study that was performed at Dr Erfan and Bagedo General hospital in Jeddah, between November 2015 and January 2018. During the study period, a total of 25 patients had sub-massive PE with a mean age of 55±04 years. 16 (60%) of the study subjects were male (figure 1).

The most frequent comorbidities were systemic hypertension (16%), coronary artery disease (12%), congestive heart failure (4%), chronic pulmonary disease (8%), active cancer (8%), previous DVT (100%), cerebrovascular stroke (16%), cesarean section (4%) and previous pulmonary embolism (4%) (table 1).

There was a significant difference between the baseline echocardiographic parameters and these parameters 48 hours after CDT in favor of the CDT (table 2). The average echocardiographic right ventricular end diastolic diameter (RVEDD) were reduced from 4.8 cm to 4 cm which is statistically significant (P < 0.05). The average echocardiographic right ventricular end-diastolic dimeter/left ventricular end-diastolic diameter ratio (RVEDD/ LVEDD ratio) decreased from baseline to 48 hours by 0.3 cm (P< 0.001); the ratio was reduced from 1.1 (range from 0.9 to 1.6) at baseline to 0.9 (range from 0.8 to 1.22) at 48 hours (figure 2). The average right ventricular systolic function were significantly improved; RV-TAPSE was 1.3 cm at baseline and became 1.8 cm 48 hours after CDT (P value < 0.05) and the baseline RV-TASV was 7.9 cm/s and became 10.5 cm/s 48 hours after CDT (P value < 0.001) (figure 3). In comparison to baseline, there was a significant reduction in systolic pulmonary artery pressure (sPAP). sPAP before treatment was 50.22 mmHg (Range from 26 to 100 mmHg) and after 48 h was 33.3 mmHg (Range from 20 to 93 mmHg) (P value < 0.05) (figure 4).
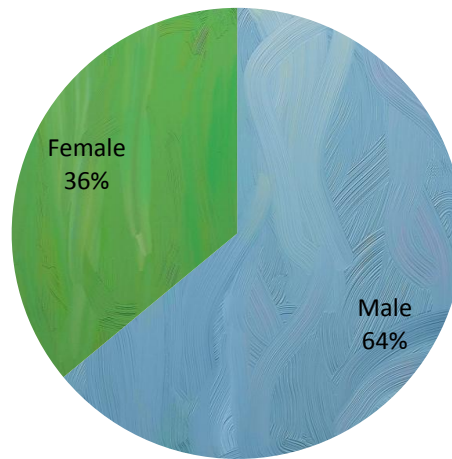
Figure (1): Male to female ratio in study patients.

Table (1): Medical history of the study patients at the baseline.

| Demographic Features	(N, %)
Age (ys)	55±04
Gender (male)	16 (60%)
Systemic Hypertension	4 (16%)
Coronary Artery Disease	3 (12%)
Congestive Heart Failure	1 (4%)
Chronic Pulmonary Disease	2 (8%)
Active Cancer	2 (8%)
Previous DVT	25 (100%)
Cerebrovascular Stroke	4 (16%)
Cesarean Section	1 (4%)
Previous Pulmonary Embolism	1 (4%)

Table (2): Echo and laboratory parameters of the study patients at the baseline and after 24 h. RVEDD, right ventricular end diastolic diameter; LVEDD, left ventricular end diastolic diameter; RV/LV, right ventricular to left ventricular

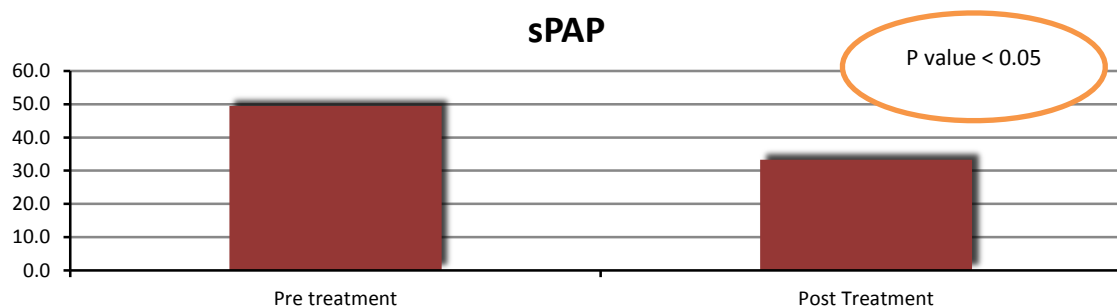|	Pre Average	Pre Minimum	Pre Maximum	Post Average	Post Minimum	Post Maximum	P value
RVEDD (cm)	4.8	3.4	6.3	4.0	3.4	4.9	< 0.05
LVEDD (cm)	4.2	3.0	5.0	4.2	3.2	4.9	0.33
RVEDD/LVEDD	1.1	0.9	1.6	0.9	0.8	1.22	< 0.001
RV-TAPSE (cm)	1.3	0.7	2.0	1.8	1.53	2.3	< 0.05
RV-TASV (cm/s)	7.9	4.8	14.3	10.5	1.4	14	< 0.001
sPAP (mmHg)	50.22	26	100	33.3	20	93	< 0.05
Troponin	73.5	0.01	513	51.7	0.01	406	
Pro-BNP	5520	55	31367	615	7.3	1827	
D-Dimer	83	0.17	881	61	0.2	703	

RVEDD; right ventricular end diastolic diameter, LVEDD; left ventricular end diastolic diameter, RVEDD/LVEDD; right ventricular end diastolic diameter/ left ventricular end diastolic diameter ratio, RVEDD; right ventricular end diastolic diameter, LVEDD; left ventricular end diastolic diameter, RVEDD/LVEDD; right ventricular end diastolic diameter/ left ventricular end diastolic diameter ratio, RV-TAPSE; right ventricular-Tricuspid annular plane systolic excursion, RV-TASV; right ventricular-Tricuspid annular systolic velocity, sPAP; systolic pulmonary artery pressure.
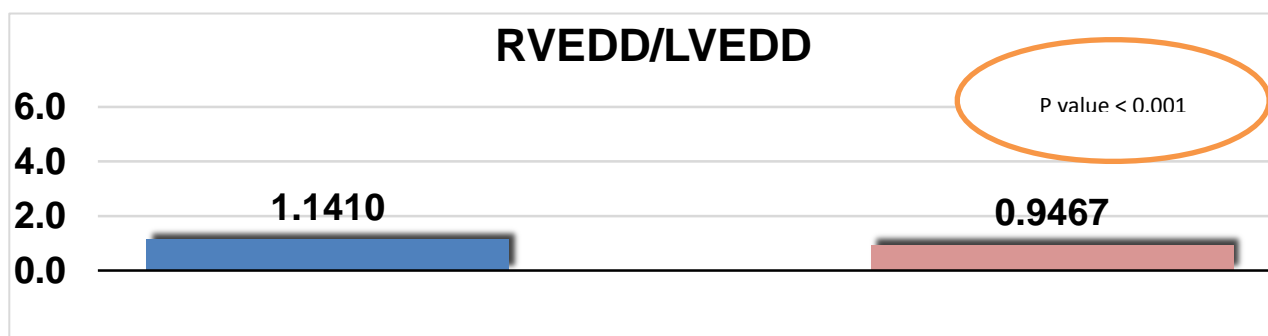
Figure (2): The average RVEDD/LVEDD ratio at baseline and after 24 hours
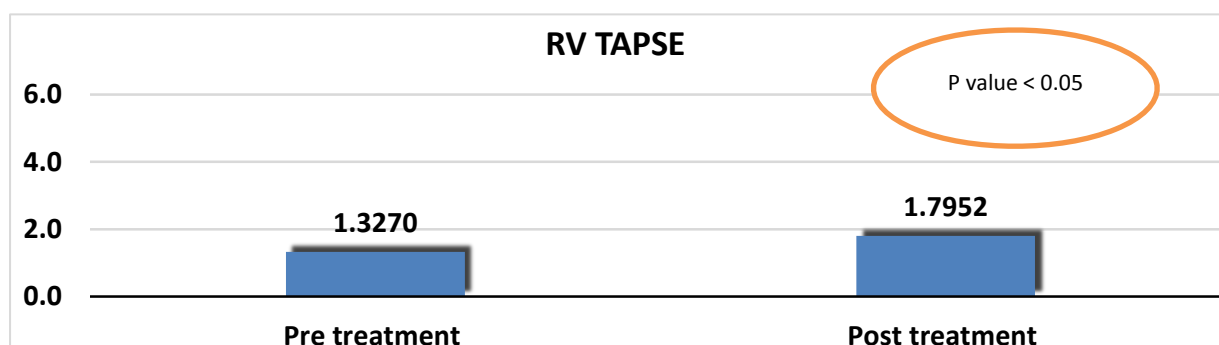
Figure (3): The average right ventricular systolic function (RV-TAPSE) at baseline and after 24 hours

Right Ventricular Reverse Remodeling after Catheter-Directed Thrombolysis for Sub-massive Acute Pulmonary

Figure (4): The average systolic pulmonary artery pressure (sPAP) at baseline and after 24 hours

Within 90 days after CDT, only 3 minor bleeding episodes but no hemodynamic decompensation, recurrent venous thrombo-embolism, major bleeding complications or death.

Discussion

The present study investigated whether CDT is effective in reversal of RV remodeling in patients with acute sub-massive PE. Cardiac biomarkers (troponin elevation or pro-brain natriuretic peptide) and imaging evidence of right ventricular dysfunction confirmed the presence of acute sub-massive PE in all study patients. The goal of revascularization therapy was to facilitate right ventricular recovery, to improve symptoms and survival, and to prevent chronic thrombo-embolic pulmonary hypertension. Kuo et al, in 2009 stated that an ideal PE reperfusion strategy should be effective in reversing RV dysfunction and reducing adverse clinical events without causing an increase in the complication rate compared with treatment with anticoagulation alone.[12] Reports of CDT suggest favourable outcomes in patients with massive and sub-massive pulmonary embolism in rapidly restoring cardio-pulmonary haemodynamics, reducing acute mortality and avoiding long-term morbidity.[14,15]

Multiple CDT techniques have been described; but we used the simplest and the most commonly performed one that is a local, slow infusion of a thrombolytic agent through low-profile catheters placed in the obstructed pulmonary artery (PA).

A fixed low-dose thrombolysis regimen; 1 mg per lung per hour rtPA over 12 hours (24 mg rtPA for bilateral PE and 12 mg for unilateral PE), was used in all patients. Delivery of the drug directly into the thrombus aiming to increase the surface area of thrombus subjected to the drug, thereby improving efficacy of thrombolysis and using smaller doses of the drug. During infusion of tPA, all patients were maintained on anticoagulation to prevent perica-theter thrombus formation and propagation of preexisting thrombus. This strategy is in line with many other studies.[16]

Increased RV/LV ratio (by echocardio-graphy or CT angiography), RVEDD and sPAP are reproducible and well-validated tools for identifying PE patients at risk of adverse outcomes.[17] Accordingly, we used changes in RV/LV ratio after CDT as surrogate marker for clinical outcomes in the treatment of PE.

The primary endpoint of the present study was the change in RVEDD, RVEDD/ LVEDD ratio and systolic pulmonary artery pressure from the time of catheter place-ment to catheter removal. In this study, the reduction of pulmonary artery systolic pressure was accompanied by an impro-vement in right ventricular systolic function with significant P value ($P < 0.05$) suggesting a reduction in pulmonary vascu-

lar resistance. An improvement in RV function is an important surrogate endpoint. Our results concordant with Kuo et.al, 2015 who stated that; in sub-massive PE patients who treated with CDT, there was a significant decrease in PA pressure and improvement in RV function, with no reported major complications, major bleeding, or strokes.[18] Piazza et.al., in 2015 reported that; there was a significant reduction in RV-to-LV diameter ratio, pulmonary artery systolic pressure and thrombus burden at 48 hours.[17]

Our study concordant with Kuo et.al., 2009, who stated that a radiographic, such as a normal-appearing angiogram, end point is generally not an acceptable end point by itself.[12]

When an invasive procedure is considered, the benefit must be weighed against the added risk. Therefore safety outcome of the present study was the complications. In our study, there were 3 minor bleeding episodes but no mortality, major bleeding complications or recurrent venous thromboembolism. A meta-analysis in 2017 evaluated 16 studies of CDT and found a major complication rate of 4.7% and intracranial hemorrhage rate of 0.35%.[19] All study patients were discharged home without oxygen. Arora et.al., compared systemic thrombolysis with CDT and demonstrated lower in-hospital mortality and bleeding in patients who received CDT.[20]

Conclusion

CDT for the treatment of acute sub-massive PE is a promising treatment option associated with immediate improvement in right ventricular dysfunction and low rates of morbidity and mortality. CDT accele-rates reversing right ventricular remodeling in patients with sub-massive PE effectively and safely. Future studies will further define the role of CDT in comparison to other revascularization strategies in the management of PE patients at increased risk.

Conflict of interest: All authors report no conflict of interest.

Address for correspondence: Abd El-Maksoud Elganady, MD, Dr Erfan and Bagdo hospital, Jeddah, Saudi Arabia. Email: elganady_1965@hotmail.com

References

1- Kasper W, Konstantinides S, Geibel A, et al., Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol. 1997; 30: 1165–1171.

2- Zeni PT, Blank BG, Peeler D W. Use of rheolytic thrombectomy in treatment of acute massive pulmonary embolism. J Vasc Interv Radiol. 2003; 14 (12):1511–1515.

3- Jaff MR, McMurtry MS, Archer SL, et al., Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011; 123: 1788–830.

4- Kucher N, Rossi E, DeRosa M, et al., Massive pulmonary embolism. Circulation. 2006; 113:577–582.

5- Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010; 38(4) (suppl): S495-S501.

6- Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. Circulation. 2010; 122: 1124–1129.

7- Stavros V. Konstantinides, Adam Torbicki. Management of pulmonary embolism: recent evidence and the new European guidelines. European Respiratory Journal 2014; 44: 1385-1390.

8- Meyer G, Vicaut E, Danays T, et al., Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370: 1402–1411.

9- Kucher N, Boekstegers P, Müller OJ, et al., Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014; 129: 479–486.

10- Melanson S, Laposata M, Camargo Jr. et al.,, "Combination of D-dimer and amino-terminal pro-B-type natriuretic peptide testing for the evaluation of dyspneic patients with and without acute pulmonary embolism," Archives of Pathology and Laboratory Medicine 2006; 130 (9): 1326–1329.

11- A. Krajina, M. Lojík, V. Chovanec et al., "Percutaneous mechanical fragmentation of emboli in the pulmonary artery," Ceska Radiologie 2007; 61 (2): 162–166.

12- Kuo WT, Gould MK, Louie JD, et al., Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol. 2009; 20: 1431–1440.

13- De Gregorio M A, Gimeno M J, Mainar A. et al., Mechanical and enzymatic thrombolysis for massive pulmonary embolism. J Vasc Interv Radiol. 2002;13(2 Pt 1):163–169.

14- Victor F, Taps-on, Keith Sterling, et al., A Randomized Trial of the Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism. The OPTALYSE PE Trial. JACC: Cardiovascular interventions 2018; 11 (14): 1401-1410.

15- Kuo WT. Endovascular therapy for acute pulmonary embolism. Journal of Vascular and Interventional Radiology. 2012; 23: 167–179.

16- Piazza G, Hohlfelder B, Jaff MR, et al., A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: The SEATTLE II Study. JACC Cardiovasc Interv. 2015; 8 (10): 1382-1392.

17- Coutance G, Cauderlier E, Ehtisham J, et al., The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care 2011;15: R103.

18- Kuo WT, Banerjee A, Kim PS, et al., Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest 2015; 148: 667–73.

19- Bloomer TL, El-Hayek GE, McDaniel MC, et al., Safety of catheter-directed thrombolysis for massive and submassive pulmonary embolism: results of a multicenter registry and meta-analysis. Catheter Cardiovasc Interv 2017; 89: 754–760.

20- Arora S, Panaich SS, Ainani N, et al., Comparison of in-hospital outcomes and readmission rates in acute pulmonary embolism between systemic and catheter-directed thromb-olysis (from the National Readmission Database). Am J Cardiol. 2017;120(9):1653-1661.